an increased half-life or greater ease of production or purification. A fusion may be direct or a linker may be inserted between the endoglin polypeptide and any other portion. A linker may be a structured or unstructured and may consist of 1, 2, 3, 4, 5, 10, 15, 20, 30, 50 or more amino acids, optionally relatively free of secondary structure. A linker may be rich in glycine and proline residues and may, for example, contain a sequence of threonine/serine and glycines (e.g., TGGG (SEQ ID NO: 31)) or simply one or more glycine residues,(e.g., GGG (SEQ ID NO: 32). Fusions to an Fc portion of an immunoglobulin or linkage to a polyoxyethylene moiety (e.g., polyethylene glycol) may be particularly useful to increase the serum half-life of the endoglin polypeptide in systemic administration (e.g., intravenous, intraarterial and intra-peritoneal administration). In certain embodiments, an endoglin-Fc fusion protein comprises a polypeptide comprising, consisting of, or consisting essentially of, an amino acid sequence that is at least 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence of amino acids starting at any of positions 26-42 of SEQ ID NO:1 and ending at any of positions 333-378 of the human endoglin sequence of SEQ ID NO:1, and optionally may not include a full-length endoglin ECD (e.g., the endoglin polypeptide may be chosen so as to not include the sequence of amino acids 379-430 of SEQ ID NO:1, or a portion thereof, or so as not to include any 5, 10, 20, 30, 40, 50, 52, 60, 70, 100, 150 or 200 or more other amino acids of any part of endoglin or any part of amino acids 379 to 581 of SEQ ID NO:1), which polypeptide is fused, either with or without an intervening linker, to an Fc portion of an immunoglobulin. An endoglin polypeptide, including an endoglin-Fc fusion protein, may bind to BMP9 and/or BMP10 with a K_D of less than 10^{-8}M, 10^{-9}M, 10^{-10}M, 10^{-11}M or less, or a dissociation constant (k_d) of less than 10^{-3} s^{-1}, 3×10^{-3} s^{-1}, 5×10^{-3} s^{-1} or 1×10^{-4} s^{-1}. The endoglin polypeptide may be selected to have a K_D for BMP9 that is less than the K_D for BMP10, optionally less by 5-fold, 10-fold, 20-fold, 30-fold, 40-fold or more. The endoglin polypeptide may have little or no substantial affinity for any or all of TGF-β1, -β2 or -β3, and may have a K_D for any or all of TGF-β1, -β2 or -β3 of greater than 10^{-9}M, 10^{-8}M, 10^{-7}M or 10^{-6}M.

[0009] An Fc portion may be selected so as to be appropriate to the organism. Optionally, the Fc portion is an Fc portion of a human IgG1. Optionally, the endoglin-Fc fusion protein comprises the amino acid sequence of any of SEQ ID NOs: 33, 34, 35, or 36. Optionally, the endoglin-Fc fusion protein is the protein produced by expression of a nucleic acid of any of SEQ ID Nos: 17, 20, 22, 24, 26, 28 or 30 in a mammalian cell line, particularly a Chinese Hamster Ovary (CHO) cell line. An endoglin polypeptide may be formulated as a pharmaceutical preparation that is substantially pyrogen free. The pharmaceutical preparation may be prepared for systemic delivery (e.g., intravenous, intraarterial or subcutaneous delivery) or local delivery (e.g., to the eye).

[0010] The endoglin polypeptides disclosed herein may be used in conjunction or sequentially with one or more additional therapeutic agents, including, for example, anti-angiogenesis agents, VEGF antagonists, anti-VEGF antibodies, anti-neoplastic compositions, cytotoxic agents, chemotherapeutic agents, anti-hormonal agents, and growth inhibitory agents. Further examples of each of the foregoing categories of molecules are provided herein.

[0011] In certain aspects, the disclosure provides methods for inhibiting angiogenesis in a mammal by administering any of the endoglin polypeptides described generally or specifically herein. The endoglin polypeptide may be delivered locally (e.g., to the eye) or systemically (e.g., intravenously, intraarterially or subcutaneously). In certain embodiments, the disclosure provides a method for inhibiting angiogenesis in the eye of a mammal by administering an endoglin polypeptide to the mammal at a location distal to the eye, e.g. by systemic administration.

[0012] In certain aspects the disclosure provides methods for treating a tumor in a mammal. Such a method may comprise administering to a mammal that has a tumor an effective amount of an endoglin polypeptide. A method may further comprise administering one or more additional agents, including, for example, anti-angiogenesis agents, VEGF antagonists, anti-VEGF antibodies, anti-neoplastic compositions, cytotoxic agents, chemotherapeutic agents, anti-hormonal agents, and growth inhibitory agents. A tumor may also be one that utilizes multiple pro-angiogenic factors, such as a tumor that is resistant to anti-VEGF therapy.

[0013] In certain aspects, the disclosure provides methods for treating patients having a BMP9 or BMP10 related disorder. Examples of such disorders are provided herein, and may include, generally, disorders of the vasculature, hypertension, and fibrotic disorders.

[0014] In certain aspects the disclosure provides ophthalmic formulations. Such formulations may comprise an endoglin polypeptide disclosed herein. In certain aspects, the disclosure provides methods for treating an angiogenesis related disease of the eye. Such methods may comprise administering systemically or to said eye a pharmaceutical formulation comprising an effective amount of an endoglin polypeptide disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. **1** shows the native amino acid sequence of human ENG, isoform 1 (L-ENG). The leader (residues 1-25) and predicted transmembrane domain (residues 587-611) are each underlined.

[0016] FIG. **2** shows the native nucleotide sequence encoding human ENG, isoform 1 (L-ENG). Sequences encoding the leader (nucleotides 414-488) and predicted transmembrane domain (nucleotides 2172-2246) are each underlined.

[0017] FIG. **3** shows the native amino acid sequence of human ENG, isoform 2 (S-ENG). The leader (residues 1-25) and predicted transmembrane domain (residues 587-611) are each underlined. Compared to isoform 1, isoform 2 has a shorter and distinct C-terminus, but the sequence of the extracellular domain (see FIG. **9**) is identical.

[0018] FIG. **4** shows the native nucleotide sequence encoding human ENG, isoform 2 (S-ENG). Sequences encoding the leader (nucleotides 414-488) and predicted transmembrane domain (nucleotides 2172-2246) are each underlined.

[0019] FIG. **5** shows the native amino acid sequence of murine ENG, isoform 1 (L-ENG). The leader (residues 1-26) and predicted transmembrane domain (residues 582-606) are underlined and bracket the extracellular domain of the mature peptide (see FIG. **10**). Isoform 3 of murine ENG (GenBank accession NM_001146348) differs from the depicted sequence only in the leader, where the threonine at